Remarks

The April 29, 2008 Office Action indicated that the priority claim had been perfected with respect to all claimed priority references, objected to an informality in the title, and raised anticipation and obviousness rejections. In view of the amendment above and arguments below, reconsideration is respectfully requested.

Informality

It is agreed that the examiner's suggestion for a modified title more accurately reflects Applicants' intentions. Hence, the above amendment incorporates the suggested change. This is believed to overcome the informality objection.

Nature Of Other Amendments

Features of claims 1, 2 and 5 have been combined and presented as new claim 17 (which now relates to a method for monitoring the activity of a dehydrogenase enzyme in a sample or measuring the amount of a substrate for this enzyme in a sample). Hence, claims 1, 2 and 5 have been cancelled to avoid redundancy, claim 3 addresses an antecedent basis issue, and corresponding dependencies in other claims are conformed.

Claim 17 also specifies that it comprises a step of providing a buffered solution comprising the sample and the dehydrogenase, NAD^+ or $NADP^+$, a NADH or NADPH reductase and a redox active agent. There is clear support for the use of a buffered solution comprising these reagents in the description as originally filed. In particular, the description includes a section entitled "Detection Methods" from page 9, line 9 to page 10, 16. This teaches that the necessary reagent mixture for carrying out the assay methods of the invention can be provided as the buffered solution now specified in claim 1 (see in particular page 9, lines 22 to 24).

This buffered solution could be used either as such, for mixing directly with the liquid sample, or alternatively it could be stored in a dried form, to be reconstituted back into the form of a buffered solution once the liquid sample is added (as described specifically at page 9, lines 22 to 30). In both cases, the assay method of the invention clearly

ultimately involves of a buffered solution comprising the various reagents and the liquid sample, as now set out in claim 1.

Analogous amendments have been made to claims 15 and 16, which are directed to electrochemical cells. Thus, these electrochemical cells comprises a reagent mixture in the form of a buffered solution. Claim 16 has also been amended to specify that it can be used to carry out a method having the specific steps set out in original claim 1.

New claims 18 and 19 are also directed to electrochemical cells. These are mostly derived from former claims 15 and 16. However, in the cells of new claims 18 and 19 the mixture of enzymes and redox agent is obtainable by drying a buffered solution comprising them. Clear basis for preparation of electrochemical cells in this way can be found at page 9, lines 22 to 30. In particular, it is described here that the mixture of enzymes and redox agent (line 30) can be obtained by depositing onto the electrode system and then drying the buffered solution (lines 22 to 25).

Claim Rejections - § 102

Former claims 1 to 6, 13, 15 and 16 were rejected as anticipated by Cosnier et al. In response, Applicants submit, for the reasons explained in more detail below and in the accompanying Declaration by inventor Wong, that the subject-matter of the amended claims is not disclosed in Cosnier et al.

The enclosed Declaration explains in paragraphs 3 to 8 the basic differences between the subject-matter claimed in the present application and that disclosed in Cosnier et al. In particular, an important feature of the assay methods of the present invention is that the reagent mixture is provided in the form of a buffered solution (i.e., the reagents are contained in a mixture with the liquid substrate-containing sample). In contrast, Cosnier et al. teaches two bio-electrode systems.

The first bioelectrode system comprises a "poly-1-Fre-electrode", which is an electrode on which flavin reductase has been immobilized by polymerisation of a mixture of the

reductase with an amphiphilic pyrrole monomer adsorbed onto the electrode surface (see section 2.2 at page 686 of Cosnier et al.). As is shown in Figure 1 of Cosnier et al., this first electrode is used in assays for the detection of NAD(P)H. The second bio-electrode system described in Cosnier et al. comprises a "poly-1-Fre-LDH-electrode", which is an electrode on which both flavin reductase and lactate dehydrogenase have been co-immobilized using an analogous immobilisation procedure (see page 687, column 1, second paragraph). This second electrode is used in assays for the detection of a lactate substrate present in a phosphate buffer solution also comprising riboflavin and NAD^+ (as shown, for example, in Figure 4 of Cosnier et al.).

Accordingly, the methods described in Cosnier et al. are carried out on electrode systems in which the assay reagents have been immobilized on the electrode surface. Thus, Cosnier et al. does not anticipate the assay method claims now on file, all of which specify that the reductase and the dehydrogenase enzyme are provided in solution together with the liquid sample.

Furthermore, none of the electrochemical cell claims are anticipated by Cosnier et al. Various electrochemical cells either comprise a buffered solution of reagents or the reagent mixture is obtainable by drying such a buffered solution. Thus, the buffered solution can be reconstituted, for example, simply by adding the liquid sample to the cell. In contrast, the cells described in Cosnier et al. differ in that reductase (and dehydrogenase enzyme) are physically immobilized in a polymerised matrix on the electrode surface. Addition of a liquid sample to such a cell would not result in formation of a buffered reagent solution; rather, the fundamental principle underlying Cosnier et al. is that the reagents remain immobilized on the electrode surface throughout operation of the cell.

In conclusion, therefore, Applicants submit that the claimed subject-matter is not anticipated by the cited prior art.

Claim Rejections - § 103

The remaining claims previously on file were held obvious based on Cosnier et al. in view of, variously, U.S. patent 6,117,661, Fredricks et al. and Bu et al. In response, Applicants submit that the feature of providing the reagents in a buffered solution, which is recited in all of the claims now on file, would not have been obvious from any of these documents. Therefore, all of the subject-matter claimed is non-obvious.

This argument is supported by the detailed comments provided in Professor Wong's Declaration. In particular, as well as explaining the important differences between the present invention and the methods disclosed in Cosnier et al., the Declaration outlines the differences from the methods of Bu et al. It will be appreciated from paragraphs 9 and 10 of the Declaration that the teaching of Bu et al. is entirely consistent with that of Cosnier et al. Specifically, it teaches that a working biosensor might be possible if the reductase at least (and preferably also other reagents) is immobilized on the electrode surface. There is no disclosure at all in Bu et al. of a biosensor in which the assay reagents are present in solution.

As is explained at paragraph 11 of the Declaration, the skilled worker would have recognized that the consistent teaching of Cosnier et al. and Bu et al. is to immobilize the assay reagents onto the electrode surface. The skilled worker would also be aware that immobilization is typically used when it is necessary to hold the reagents in close proximity to the electrode to ensure an adequate reaction and/or to protect reagent enzymes against degradation.

Consequently, the skilled worker would appreciate that, mostly likely for one or both of these reasons, Cosnier et al. and Bu et al. indicate that immobilization of assay reagents onto an electrode surface would be essential in order to obtain a workable dehydrogenase-based biosensor. The skilled worker would further understand from these documents that an assay system based on a substrate/dehydrogenase/NAD(P)H/ reductase/redox agent cascade in which the reagents are not

immobilized, but are instead present in a buffered solution, would not be feasible.

Thus, in the light of the teachings of Cosnier et al. and Bu et al. it is clearly surprising that the assay systems of the present invention, which are based on providing a buffered reagent solution, are successful. Further evidence that the claimed subject-matter is non-obvious is provided by the fact that the present inventors have found that it achieves important technical advantages. Some of these advantages are described in Professor Wong's Declaration (at paragraphs 12 to 14 and in its Annex). Thus, there are significant advantages in terms of reduced preparation costs. Furthermore, the concentration ranges over which the assay methods of the present invention are capable of quantitating a substrate are dramatically improved compared to Cosnier et al. and Bu et al.

Finally, Applicants submit that neither Fredericks et al. nor Wong et al. disclose electrochemical assay methods of any sort, let alone electrochemical assay methods based on a substrate/dehydrogenase/NAD(P)H/reductase/redox agent cascade wherein all of these reagents are present in solution during the assay. Accordingly, neither of these documents are capable of remedying the deficiencies of Cosnier et al. and/or Bu et al.

In summary, there is no suggestion in the prior art that the dehydrogenase-enzyme-based assay systems of the present invention would be feasible when using a buffered reagent solution, as specified in the present claims (rather, the assay systems taught in Cosnier et al. and Bu et al. teach that reagent immobilization on the electrode surface is essential to achieve a working biosensor). Furthermore, the arrangement claimed in the present application, in which all assay reagents are present in solution, enables important technical advantages as compared with the systems taught in these prior art documents. Accordingly, Applicants submit that the claimed subject-matter is non-obvious.

Conclusion

As such, reconsideration and allowance are respectfully requested of claims 3-4 and 6-16, and allowance is

respectfully requested with respect to claims 17-19. Accompanying this amendment is a petition for a three month extension of time to respond. The PTO may also charge the fee for the two additional independent claims, plus any other needed fees, to Deposit Account 17-0055.

Respectfully submitted,

LUET L. WONG ET AL.

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